

GENERAL INDEX

	PAGE
COCK'S-COMB TEST	6
DOSAGE	12-15
ERGOT FUNGUS	1
ERGOTININE... ..	2
ERGOTOXINE	2, 3
ERGOTOXINE NOT THE ONLY ACTIVE PRINCIPLE OF ERGOT	3
'ERNUTIN'	6, 8, 16
'ERNUTIN' IN HÆMORRHAGES	13
'ERNUTIN' IN NERVOUS AFFECTIONS... ..	14
'ERNUTIN' IN POST-PARTUM HÆMORRHAGE	11
'ERNUTIN' UNIFORMLY ACTIVE	8
<i>p</i> -HYDROXYPHENYLETHYLAMINE	3, 15
KYMOGRAPHIC TRACINGS	7, 9
METHODS OF STANDARDISATION	5-8
PHARMACEUTICAL ADVANTAGES OF 'ERNUTIN'	11
PHYSIOLOGICAL STANDARDISATION OF 'ERNUTIN'... ..	6
RELATION OF ERGOTOXINE TO ERGOTININE	3
SUPERIORITY OF 'ERNUTIN'	11
'TABLOID' HYPODERMIC PRODUCTS OF ERGOTOXINE	15
'TYRAMINE'	15
'VAPOROLE' 'ERNUTIN'	15, 16

The words 'TABLOID,' 'ERNUTIN,' 'TYRAMINE' and 'VAPOROLE' are brands which designate fine products issued by Burroughs Wellcome & Co. To ensure the supply of pure and reliable products, these brands should always be specified when prescribing or ordering.



22502701831

FROM ERGOT TO 'ERNUTIN'

WHEN rye is grown in poor soil, it is liable, in wet seasons or in damp foggy districts, to be affected by a parasitic fungus, known as *Claviceps purpurea*.

Ergot is the resting form of this fungus, being the sclerotium, compact mycelium or spawn which is formed in the ovary of various grasses.

It is now obtained almost exclusively from rye (*Secale cereale*), but the same or a similar fungus may affect other species of grasses. The occurrence of this fungus is not limited, however, to rye grown in wet or damp districts; spurred or ergotised rye may grow on dry gravel soil, so that moisture may play only a subsidiary part in the production of the fungus.

Ergot
a fungus

On germination the sclerotium forms spores, which are blown about by the wind and infect the young ovary of the grass flower; the parasitic fungus at first forms only a loose mycelium, which bears vegetative reproductive cells (conidia), and which secretes a sweet sticky substance ("Honey dew"). Insects, attracted by this secretion, bring about the transference of the conidia to ovaries which have previously escaped infection.

Stages of
growth

After the flowering period the fungus begins its great and final development. The mycelium becomes much more compact, and the young rye grains harden and become dry from the base upwards. At the expense of the food material intended for the young grain, the fungus grows out to the well-known reddish-brown, slightly-curved sclerotium, which falls to the ground in autumn, to germinate in the following spring.

CHEMISTRY

There is probably no drug in the pharmacopœia which has been more frequently the subject of chemical investigation than ergot. The earlier investigators made careful examinations of the inert constituents, but such physiologically-active preparations as they obtained were crude resinous mixtures which the discoverers regarded as acids or alkaloids, according to the methods of preparation.

**Early
chemical
investigations**

**Confusion
in results**

Unfortunately, in not a few instances, names suggestive of chemically-isolated principles were applied to these impure resins, and the literature on the subject has been encumbered and confused by names such as ergotin, ecbolin, sclerotinic acid, sphacelinic acid, cornutin. The nomenclature has been further complicated by the fact that some of the names, such as ergotin, have at different times been applied to a large number of substances and extracts of widely different nature.

**Complicated
nomenclature**

The first approach to the isolation of a pure active principle from ergot was made by Tanret, who in 1875 described the crystalline alkaloid ergotinine, and an amorphous alkaloid which he regarded as a mere physical modification of the crystalline variety. Although a good deal of clinical evidence seemed to support Tanret's view that, in ergotinine, he had isolated the active therapeutic principle of ergot, pharmacological experiments, such as those of Kobert, made with the pure crystalline alkaloid, showed it to be inert. Recently

**Tanret's
ergotinine**

Ergotoxine

this apparent discrepancy has been explained by the isolation of the closely-related and highly-active alkaloid "Ergotoxine," which, though itself

amorphous, can, in the form of its crystalline salts, be prepared in a state of chemical purity (*see* Barger and Carr, *Chem. News*, xciv, p. 89, 1906; *Journ. Chem. Soc.* xci, p. 337, 1907). It has been shown that ergotoxine ($C_{35}H_{41}O_6N_5$) is the hydrate of Tanret's crystalline ergotinine ($C_{35}H_{39}O_5N_5$), and that either alkaloid can easily be converted into the other. In particular it is important to note that in the solutions of ergotinine salts, ergotoxine is gradually formed, imparting to the solution an activity not possessed by the pure ergotinine. It has further been shown that the activity of various so-called active principles, such as sphacelinic acid, chrysotoxin, etc., is entirely due to the presence of adherent ergotoxine.

Relation to
Tanret's
ergotinine

The acceptance of ergotoxine as the sole active principle of ergot was made impossible by the observation that certain specimens of watery extracts produced a physiological effect on the blood-pressure and uterus far too great to be accounted for by the ergotoxine which they contained. It has recently been shown that such extracts owe most of their activity to *p*-hydroxyphenylethylamine ($OH \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot NH_2$), a small quantity of *isoamylamine* also contributing to the effect (Barger and Dale, *Journ. Physiol.*; *Proc. Phys. Soc.*, May 15, 1909).

PHARMACOLOGY

The primary action of the salts of ergotoxine, as seen in laboratory experiments, is that which has so long been associated with the pharmacological and therapeutic action of ergot, viz., a stimulation to contraction of organs and tissues containing plain muscle, in particular of the arteries and the uterus. There is evidence in favour of the view that this effect

Action of
ergotoxine

is produced by a stimulation of those terminal structures, associated with innervation by the true sympathetic system, which are the seat of action of the supra-renal active principle. It is certain that, in larger toxic doses, ergotoxine has a specific paralytic

action on this terminal apparatus, so that an injection of a supra-renal preparation, such as 'Hemisine,' then causes a fall in place of the customary rise of blood-pressure, relaxation instead of contraction of the uterus (see Dale, *Journ. Physiol.*, xxxiv., p. 163, 1906; Barger and Dale, *Bio-Chem. Journ.*, II, Nos. 5 and 6),

So characteristic is this action that it can be used as a means of recognising the presence and estimating the amount of ergotoxine in any preparation from

ergot. Another characteristic effect, but one far less susceptible of quantitative appreciation, is produced by slow administration of the alkaloid. This is the

peripheral gangrene, which figured so largely in the mediæval epidemics of ergotism, and which, especially as exhibited in the cock, has long been applied as a rough test of the activity of ergot preparations.

p-Hydroxyphenylethylamine, the chief water-soluble active constituent of ergot, has a marked resemblance in its action, as in its chemical constitution, to the supra-renal active principle. Its action differs from that of the latter in being gentler and more prolonged, and is further prolonged by association with small doses of ergotoxine.

Both laboratory experiment and the results of clinical trial have already made it abundantly evident that both ergotoxine and *p*-hydroxyphenylethylamine in appropriate doses produce the effects for which ergot is

prescribed. The dose, moreover, whether these active principles are administered as pure salts or in a preparation such as 'Ernutin,' can be regulated with a degree of accuracy which has been out of the question in dealing with crude extracts.

Accurate
dosage

STANDARDISATION

The chemistry of ergot has until recently been in a very unsatisfactory condition, and this has been reflected in the pharmacy and in the pharmacology of the drug. Authorities have repeatedly voiced the dissatisfaction felt by clinicians as the result of their experience with various ergot preparations. "Many of the samples in daily use on the market are worthless; they either have no action, or their action is of such a feeble nature as to render them useless. A properly standardised ergot is absolutely necessary." Again, "by far the greater number of these (extracts of ergot) on the market are quite valueless, in that they possess little or no power of constricting vessels or exciting the uterus to contract. Occasionally, however, a very active sample may be met with, and it is suggested that the rare cases of poisoning which have been described after the administration of medicinal quantities of ergot are caused by the use of such a sample." The variation in the composition of different ergots has been advanced as a cause of the difference in type of the various epidemics of ergotism. The unstable principles may also alter in activity, or may be removed, during the processes of manufacture of pharmaceutical preparations, so that an active sample of the drug may yield an inert extract.

Unsatisfactory
preparations

Many extracts
quite worthless

A chemical method of assaying ergot has not yet

been devised. Even the isolation from it of ergotoxine and of *p*-hydroxyphenylethylamine has not provided a

No method of chemical assay satisfactory solution of the difficulty, since these principles cannot yet be separated quantitatively from the other constituents of ergot. Various methods of physiologically assaying the drug have been suggested. The liability of birds to ergot gangrene has been known since the

Cock's-comb test time of Thuillier (1630), and many of the investigators of the chemistry of the drug have used the action on the cock's comb as a test of the activity of their preparations (Wiggers, 1831; Bonjean, 1842; Kobert, 1884, etc.). From what has been said already it is evident that all these

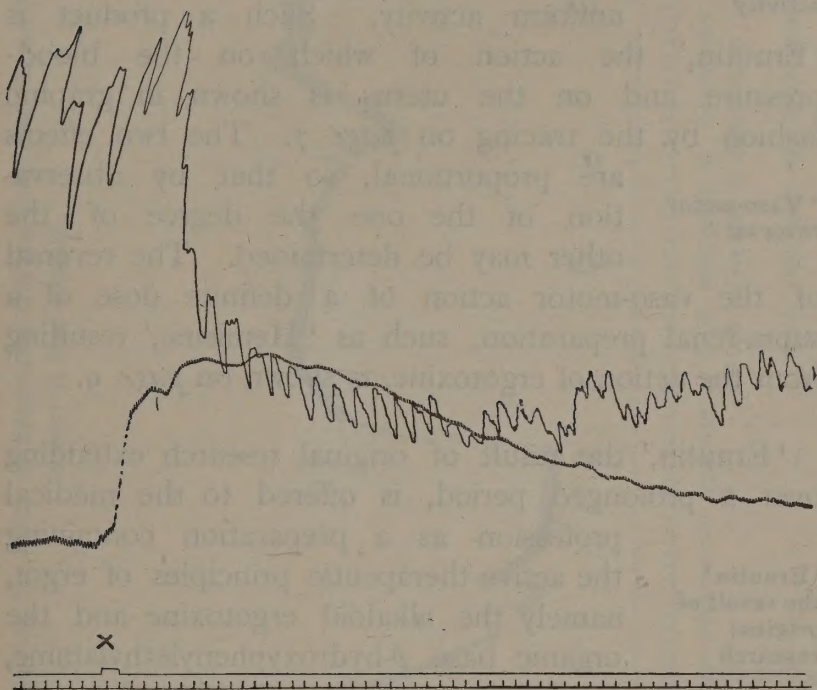
Rough and inaccurate observers were in reality making a rough test for ergotoxine, and the inaccuracy of the method—the difficulty of its quantitative interpretation—probably had much to do with the delay in recognising the true nature of the active principle. The cock's-comb test, in fact, tells little more than that a certain specimen of ergot does or does not contain ergotoxine. There can be no accurate standardisation, of pharmacological and therapeutic value, by means of this test. Another method suggested is that of observing the rise of

Effect on blood-pressure blood-pressure produced by intravenous injection. This furnishes a rough indication of the amount of *p*-hydroxyphenylethylamine, in most cases rather a small one, present in such a preparation as the official liquid extract.

In 'Ernutin,' which contains also the highly-active principle ergotoxine, it is especially important that this principle should be accurately assayed. This is rendered possible by observation of the very characteristic action (*described on pages 3, 4*) on the terminal motor elements of the sympathetic system.

KYMOGRAPHIC TRACING showing the prolonged rise of blood-pressure and the lasting contraction of the uterus

following injection of 'ERNUTIN'



X Injection of 'ERNUTIN'

Time marker shows intervals of ten seconds

'Ernutin' is therefore standardised by observation of its action on the blood-pressure, and the proportion of ergotoxine present is quantitatively estimated by determining the dose necessary to reverse the vaso-motor action of a given dose of the supra-renal active principle (*see pages 3, 4*). It is possible, by this scientific method, to obtain a product of precise and uniform activity. Such a product is 'Ernutin,' the action of which on the blood-pressure and on the uterus is shown in graphic fashion by the tracing on *page 7*. The two effects are proportional, so that by observation of the one the degree of the other may be determined. The reversal of the vaso-motor action of a definite dose of a supra-renal preparation, such as 'Hemisine,' resulting from the action of ergotoxine, is shown on *page 9*.

'Ernutin,' the result of original research extending over a prolonged period, is offered to the medical profession as a preparation containing the active therapeutic principles of ergot, namely the alkaloid ergotoxine and the organic base *p*-hydroxyphenylethylamine, in definite amount, and free from the paralytic and depressor principles associated with many ergot preparations. 'Ernutin' marks a great advance; it renders possible accuracy in therapeutics where previously there was uncertainty. The physician is assured of uniform results. A product which always contracts a flaccid uterus and arrests post-partum hæmorrhage will be appreciated by physicians whose patients and whose practice have suffered from the variability of the ergot preparations hitherto in use.

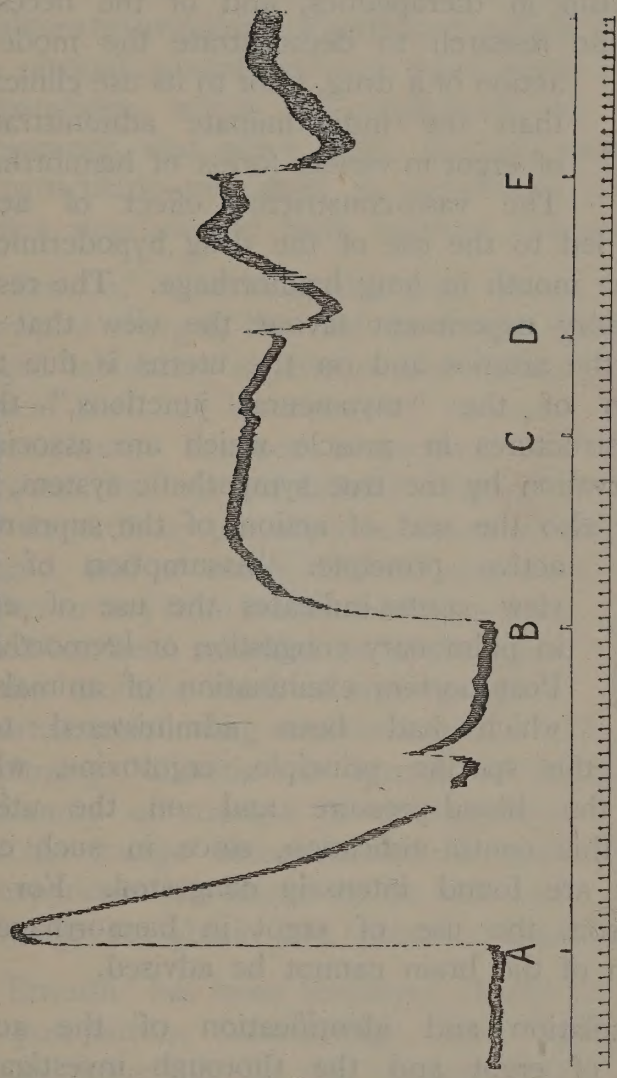
Precise
uniform
activity

"Vaso-motor
reversal"

'Ernutin'
the result of
original
research

Active
principles
produce
accurate
therapeutics

KYMOGRAPHIC TRACING showing the action of Ergotoxine and the method of standardisation of 'ERNUTIN' for amount of that alkaloid



At	A—	intravenous injection of	0.05 milligram of 'Hemisine'
"	B—	"	" 0.5 milligram of Ergotoxine
"	C—	"	" "
"	D—	"	" 0.05 milligram of 'Hemisine'
"	E—	"	" "

THERAPEUTICS

No better example can be found of the danger of empiricism in therapeutics, and of the necessity for scientific research to demonstrate the mode of action of a drug, prior to its use clinically, than the indiscriminate administration of ergot in various forms of hæmorrhage.

**Danger of
empiricism in
therapeutics**

The vaso-constrictor effect of active ergot has led to the use of the drug hypodermically and by the mouth in lung hæmorrhage. The results of laboratory experiment favour the view that the effect on the arteries and on the uterus is due to a stimulation of the "myo-neural junctions," those terminal structures in muscle which are associated with innervation by the true sympathetic system, and which are also the seat of action of the supra-renal active principle. Assumption of this

**Danger of
ergot in
hæmoptysis
and cerebral
hæmorrhage**

view contra-indicates the use of ergot in pulmonary congestion or hæmorrhage. Post-mortem examination of animals to which had been administered toxic doses of the specific principle, ergotoxine, which acts on the blood-pressure and on the uterus, confirms this contra-indication, since in such cases the lungs are found intensely congested. For the same reason, the use of ergot in hæmorrhage or congestion of the brain cannot be advised.

The isolation and identification of the active principles of ergot and the thorough investigation of their pharmacological action now render it possible to remove the therapeutics of ergot from the realm of empiricism and to place treatment by this drug on a rational basis.

**Rational
therapeutics
of ergot now
possible**

'Ernutin' embodies the results of the latest researches. It is presented as a clear, pellucid liquid, pleasant and palatable for mouth administration, whilst its use hypodermically produces no irritation. Pharmaceutically it has obvious advantages over other ergot preparations, which are unpleasant in appearance, and which often produce nausea. This is particularly important in parturition, where anæsthetics may already have induced sickness.

**A
pharma-
ceutical
advance**

'Ernutin,' containing the pure active therapeutic principles of ergot, has had its dosage fixed after prolonged laboratory experience and careful clinical trial. It is impossible to make a comparison between a product like 'Ernutin,' uniform and definite in strength, and the ordinary preparations, whose activity cannot be gauged, and of which different specimens have been shown to vary from inertness to an activity which has been surmised to be the cause of the sporadic cases of ergot gangrene reported as following medicinal doses. The physician employing 'Ernutin' is assured of the degree and uniformity of strength of the product, and the dosage recommended is such as experience has shown to be safe and sufficient to obtain the pharmacological action.

**Active
therapeutic
principles**

**Impossi-
bility of
comparisons**

**Uniform
activity**

'Ernutin' has been employed chiefly for the arrest of post-partum hæmorrhage, and various clinical reports prove that for this purpose it is superior to the ergot preparations previously employed. It promptly produces a firm contraction of the uterine muscle, and has been described as saving life when every other means had failed.

**Post-partum
hæmorrhage**

To obtain a rapid result in such cases, 'Ernutin' should be administered intramuscularly, generally in the gluteal region. 'Vaporole' 'Ernutin,' which is a sterile preparation, issued in hermetically-sealed amber-coloured containers of 10 minims and 0.6 c.c. respectively, is advised for this purpose. The dose usually given is 5 to 10 minims, and, when the condition requires it, a further dose of 5 to 10 minims may be injected in twenty minutes. It is advisable in all cases not to administer 'Ernutin' till labour be completed. After the expulsion of the placenta, an injection of 5 to 10 minims of 'Vaporole' 'Ernutin' prevents or arrests hæmorrhage, improves the tone, and assists the involution, of the uterus.

Oral administration may also be usefully employed in obstetric cases. 'Ernutin' (Oral) is issued in amber-coloured bottles of 1 oz., 4 oz., 16 oz., and 30 c.c., and may be given in doses of 30 to 60 minims every three hours after completion of the third stage of labour.

'Ernutin' acts beneficially in labour cases, not only by its effect on the uterus, but also by its power of raising the blood-pressure, which is very low in cases of shock, such as may be present after prolonged labour, instrumental and other operative interference, or post-partum hæmorrhage. This suggests the use of 'Ernutin' in other surgical operations.

When intravenous injections of saline solution are given for shock or collapse, the addition of 5—10 minims of 'Vaporole' 'Ernutin' will increase the value of the injection.

The stimulant effect of 'Ernutin' on the uterus is of value in cases of sub-involution, fibroid, metrorrhagia,

menorrhagia, dysmenorrhœa, chronic endometritis, leucorrhœa, and after curetting. Mouth administration is advisable in all these conditions, and after the use of the curette a hypodermic or intramuscular injection should also be given.

Uterine
affections

Whilst the value of 'Ernutin' in various uterine conditions may be regarded as thoroughly established, its use in other affections in which ergot has been administered must be considered as yet undecided. Where the preparations of ergot hitherto in use have been employed, the physician may with equal confidence prescribe 'Ernutin.' The danger of ergot in brain and lung hæmorrhages has already been pointed out. The value of the drug to arrest intestinal hæmorrhage is debated. The congested appearance of the bowel in cases of ergotism has prompted Ehlers and others to deprecate its use in hæmorrhage in typhoid fever. Laboratory experience shows that 'Ernutin' has a marked action in causing contraction of the intestinal arteries, and it is probable that in arterial hæmorrhage from the bowel, administration of 'Ernutin' will tend to stop the bleeding. Should the hæmorrhage be venous, 'Ernutin' is less likely to be beneficial; indeed, it might prove unsafe.

Intestinal
hæmorrhage

The structure of the prostate, which organ is largely composed of unstriped muscular fibres analogous to those of the uterus, and the idea that the prostate may be regarded as the "male uterus," have led to the use of ergot in chronic prostatitis. One author has found that ergot reduces the secretion of prostatic mucus, and that the enlarged organ diminishes in size under the treatment. For such a purpose 'Ernutin,' by

In
prostatitis

reason of its powerful action on plain muscular tissue, is the ergot preparation which should be prescribed.

Ergot has been largely employed in various affections where nervous symptoms are prominent. In exophthalmic goitre, 'Ernutin' (Oral) may be given in doses of 30 to 60 minims three or four times daily. Similar doses may be administered in chorea,—either alone or in conjunction with arsenic,—in hysteria and in diabetes insipidus.

**Nervous
affections**

Epistaxis which resisted other treatment has been observed to cease after the exhibition of 'Ernutin.' Other external hæmorrhages may be treated by administration of the drug, but its use in various internal hæmorrhages, as indicated above, must be very carefully considered. 'Ernutin' may also be employed in the treatment of enuresis, and of spermatorrhœa.

Epistaxis

Clinically, intramuscular injection of 'Vaporole' 'Ernutin' has been reported to be valuable as a cardiac stimulant in chloroform syncope. It will readily be understood that in some conditions the rise of blood-pressure consequent on the administration of 'Ernutin' may benefit the heart's action, whilst it is equally certain that in other cases the vaso-motor effect will be detrimental to the cardiac condition.

**Effect on
the heart**

Reference has already been made to the question of dosage. It may be stated that 'Vaporole' 'Ernutin' can be administered with safety in doses up to 10 minims, and that such a dose may be repeated at intervals of twenty minutes, till three doses in all (a maximum total of 30 minims) have been given. Further doses will depend on the reaction of the patient. 'Ernutin' (Oral)

Dosage

may be taken three or four times daily, in doses of 30 to 60 minims. This may be continued for some days. The effect on the pulse and on the blood-pressure should be regularly observed. A hyper-normal blood-pressure, or a slow, hard, thready, high-tension pulse, are signs which should lead to the treatment being discontinued.

Warning
symptoms

Whilst 'Ernutin' is the product generally recommended for clinical use, some may desire to employ the alkaloid ergotoxine, or *p*-hydroxyphenylethylamine. 'Tabloid' Hypodermic products present these principles in a soluble condition and in a state of chemical purity. 'Tabloid' Hypodermic Ergotoxine is given in doses of gr. 1/100 to gr. 1/50; 'Tabloid' Hypodermic 'Tyramine' (*p*-hydroxyphenylethylamine) in doses of gr. 1/30 to gr. 1/10. The administration may be repeated in the same way as with 'Vaporole' 'Ernutin,' described on page 14. Combinations of ergotoxine with strychnine and with morphine are also prepared, which meet special indications.

Ergotoxine
and
'Tyramine'

Combinations

METHOD OF FILLING SYRINGE WITH 'VAPOROLE' 'ERNUTIN'

DIRECTION.—Shake the liquid down into the bulb, and break off the neck at the file-mark. (Fig. 1).

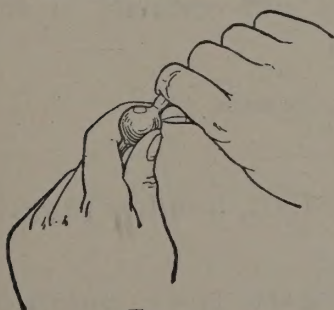


FIG. 1

Introduce the needle into the well of the bulb, and draw up the required quantity of 'Ernutin' into the syringe. (Fig 2).

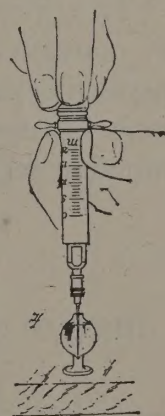


FIG. 2

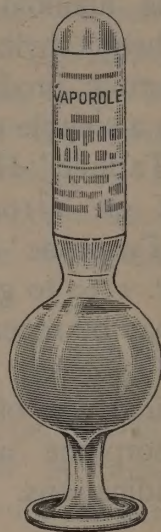
For particulars of 'Vaporole' 'Ernutin,' see next page

TRADE
MARK

'ERNUTIN' PREPARATIONS

'ERNUTIN' (Oral)—issued in 1 oz., 4 oz., 16 oz. and 30 c.c. bottles of amber-coloured glass. The active principles of ergot should not be exposed to the action of sunlight; the amber-coloured bottle has, therefore, obvious advantages. For greater convenience in use the bottles are lipped, thus facilitating the measurement of accurate doses.

'VAPOROLE' 'ERNUTIN'—issued in boxes of six amber-coloured hermetically-sealed phials. Sterile, and eminently suitable for hypodermic or intramuscular injection. Intramuscular injection is to be preferred when it is desired to obtain an immediate effect, as in post-partum hæmorrhage. As 'VAPOROLE' 'ERNUTIN' is a very potent preparation, its administration must be carefully guarded. It is suggested that the initial dose should not exceed 5 minims or 0.3 c.c.



'Vaporole'
'Ernutin'
(Registered
Design No. 542164)

The 'VAPOROLE' container is unique in construction and convenience. It perfectly preserves its contents, and may be opened with readiness and certainty at the moment required.

For dosage and directions, see pages 12-15

BURROUGHS WELLCOME & CO., London (Eng.)

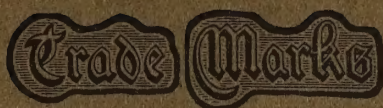
Branches:

NEW YORK MONTREAL SYDNEY CAPE TOWN SHANGHAI

1495 *h/a/i/s/c/u/e*

[ALL RIGHTS RESERVED]

THE



'Tabloid'

AND

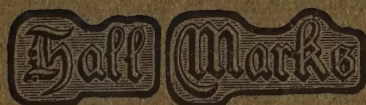
'Soloid'

Invented

by

B. W. & Co.

Are
B. W. & Co.



They *mark* the work of

Burroughs Wellcome & Co.

They *mean* "Issued by

Burroughs Wellcome & Co."

They *stand* for



products

